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(54) Title: CRYSTALLIZATION OF BETA–LACTAM COMPOUNDS

(57) Abstract

A process for the crystallization of β–lactam compounds involving simultaneous addition of a solution of said β–lactam compound and a titrant to a crystallization vessel. In case of zwitterionic β–lactam compounds, the pH–value is maintained between 2.5 and 7.5, preferably between the isoelectric point of said compound and 7.5 and at a temperature between 0 °C et 50 °C.

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CRYSTALLIZATION OF BETA-LACTAM COMPOUNDS

Field of the invention

The present invention relates to a new process for the crystallization of ß-lactam compounds.

It is commonly accepted that the most economical approach for the isolation of compounds such as ß-lactam antibiotics or their intermediates from their corresponding aqueous solutions is crystallization. For example in United States patent US 4,248,780 it has been described that the zwitterionic antibiotic ampicillin has been isolated from an aqueous solution containing the hydrochloride salt of ampicillin by adding gradually an aqueous base until the pH has reached a value of 4.5 to 5.3 followed by filtration of the ampicillin trihydrate crystals. The antibiotics amoxicillin, ampicillin and cephalexin are similarly obtained as described in European patent application EP 0011513 B. A major drawback of this crystallization procedure is the fact that it is carried out in a discontinuous way in batch processes and therefore difficult to control. Crystallization of unwanted by-products can thus occur at any stage of the crystallization procedure. Furthermore, as result of a discontinuous operation, often a wide range of crystal size distribution occurs. Another drawback of the crystallization process is that the crystalline products contain unacceptably high levels of hydrochloric acid salts.

Surprisingly it has been found that ß-lactam antibiotics can be crystallized through a different process comprising simultaneous addition of a ß-lactam compound and a corresponding titrant to a crystallization vessel. This method has not previously been described or suggested for ß-lactams until now.

Summary of the invention

The present invention provides a process to prepare a crystalline ß-lactam compound which comprises simultaneous addition of a solution of said ß-lactam compound and a corresponding titrant to a crystallization vessel to form a crystallization mixture and isolation of the crystalline ß-lactam compound.

The ß-lactam compounds are crystallized from a crystallization reaction mixture or from a solution of said ß-lactam compound in water or in a mixture of water and one or more organic solvents. The ß-lactam compounds are for example penicillins, cephalosporins and clavams.

Examples of penicillins are amoxicillin, ampicillin, epicillin and 6ß-aminopenicillanic acid (6-APA).

Examples of cephalosporins are cefaclor, cefadroxil, cefprozil, cefetamet, cefotaxim, cephalexin, cephaloglycin, cephradine, 7ß-aminocephalosporanic acid (7-ACA), 7ß-amino-3-chloro-3-(desacetoxymethyl)cephalosporanic acid (7-ACCA), 7ß-amino-3'-desacetoxymethylcephalosporanic acid (7-ADCA) and 7ß-amino-3'-desacetyl-cephalosporanic acid (7-ADAC).

Examples of clavams are for instance amine salts of clavams as t-butylamine clavulanate, t-octylamine clavulanate, bis(2-(dimethylamino)ethyl) ether diclavulanate, N,N,N',N'-tetramethyl-1,2-diaminoethane mono-clavulanate or N,N,N',N'-tetramethyl-1,2-diaminoethane diclavulanate.

Detailed description of the invention

The crystallization process according to the present invention comprises of optionally placing a small amount of solvent or crystallization reaction mixture of the ß-lactam compound (0-10%) in a crystallization vessel followed

by simultaneous and separate addition of a solution of the said ß-lactam compound and a titrant.

A solution of the ß-lactam compound can be obtained:

by dissolving the ß-lactam compound or a salt or an acidic addition salt thereof in an acidic medium or

by dissolving the ß-lactam in an alkaline salt form in water and/or an organic solvent, if necessary in alkaline medium or

by dissolving the ß-lactam in the free acid form in an acidic medium in water and/or an organic solvent.

The corresponding titrant is defined in the present application as the acid or base which neutralises the ß-lactam compound in the obtained solution and/or brings the ß-lactam compound in the desired form. The titrant is optionally mixed with a solvent, and the concentration may vary between about 0.01 M to about 13 M when aqueous solutions are used, depending upon the scale of the condensation reaction. The acid titrant is an inorganic acid, preferably anyone of the groups consisting of hydrochloric acid, sulphuric acid, nitric acid and phosphoric acid or an organic acid preferably formic acid or acetic acid. The base titrant is an inorganic base, preferably anyone of the groups consisting of sodium hydroxide, potassium hydroxide and ammonium hydroxide or an organic base, preferably an amine, as for instance monoamine, preferably tertiary butylamine, tertiary octylamine, benzhydrylamine or a diamine, preferably N,N'-diisopropylethylenediamine, N,N,N',N'-tetramethyl-1,2- diaminoethane or bis(2-(dimethylamino)ethyl)ether.

In case the ß-lactam compound is a zwitterionic antibiotic, the pH-value is adjusted between 2.5 and 7.5, more specifically between the isoelectric point of the ß-lactam compound and 7.5 by adding an acid or a base. Furthermore, seeding material may be added to the crystallization vessel before the addition of said compound and the titrant. The temperature of the crystalline vessel is preferably maintained between 0°C and 50°C and more specifically between 0°C and 30°C. Subsequently, both the bulk of the solution of the ß-lactam compound and a suitable titrant are added

simultaneously at such a ratio that the pH-value remains within the range as set above.

Accordingly, after filtration and drying crystalline products are obtained that contain no more than 1% of unwanted by-products such as acid salt of the same ß-lactam compounds whereas known procedures give impurity levels of 3.5 to 9%. Another advantage of the present crystallization process is that it is easy to control as batch wise addition is avoided. Furthermore, as a result of continuous process operation the crystal size distribution can be minimized.

The present invention is particularly suitable for the preparation of ß-lactam antibiotics and intermediates in the form of zwitterionic amino acid. Examples of said intermediates are 6ß-aminopenicillanic acid (6-APA), 7ß-aminocephalosporanic acid (7-ACA), 7ß-amino-3-chloro-3-(desacetoxymethyl)cephalosporanic acid (7-ACCA), 7ß-amino-3'-desacetoxycephalosporanic acid (7-ADCA), 7ß-amino-3'-desacetylcephalosporanic acid (7-ADAC), cephalosporin-C and salts thereof. These ß-lactam compounds may be produced from the fermentation products penicillin-G or penicillin-V respectively by chemical means as described in Belgium patent BE 718824 and Recl. Trav. Pays-Bas 112, 66 (1993) or by an enzymatic conversion as described in European patents EP 283218, EP 322032 and EP 436355B, French patent application FR 2241557, United States patents US 4,141,790 and US 3,960,662 and International patent application WO 90/12110. 7-ADCA can be produced from 7-ACA as described in European patent EP 454478B, US patents US 3,304,236 and US 3,972,774. Furthermore, 7-ADCA, 7-ADAC and 7-ACA can be produced by fermentation followed by enzymatic conversion as described in European patent applications EP 532341 and EP 540210.

Examples of said zwitterionic antibiotics are amoxicillin, ampicillin, epicillin, cefaclor, cefadroxil, cefetamet, cefotaxim, cefprozil, cephalexin, cephaloglycin and cephradine. These antibiotics can be produced from ß-lactam intermediates such as 6-APA, 7-ACA, 7-ACCA, 7-ADAC, 7-ADCA

and alpha-substituted phenylacetic acid derivatives, either chemically as described in Recl. Trav. Chim. Pays-Bas 112, 66 (1993) and references cited therein or enzymatically as described in International patent application WO 97/04086.

The process of crystallization of antibiotic compounds, according to the present invention, provides various advantages over the existing methods.

In the first place better concordance results have been obtained. The concordance value which is related to the difference between titration with a strong acid and titration with a strong base has been defined according to the United States Pharmacopeia, twenty-first revision, Official from 1 January 1985. A small concordance value stands for a constant quality product, for example, ampicillin trihydrate, isolated from crystallization of a solution containing ampicillin hydrochloride by adding a base has a concordance value of less than 1 mol %, while crystallization through a normal procedure of a number of experiments has given a concordance value between 4 and 8 mol %. The ß-lactam antibiotic compounds with a small concordance value, i.e. comprising for example lower amounts of acid salt of the corresponding ß-lactam antibiotics, are suitable for pharmaceutical formulation purposes. The present invention provides also a better stability of the ß-lactam antibiotic due to short stay of the ß-lactam antibiotic in solution during the crystallization process. Furthermore, a uniform particle size distribution provides better quality of the ß-lactam antibiotic compounds.

The preparation of amine clavam, for example amine clavulanate according to the present invention, does not require the adjustment of pH-values because the clavulanic acid is not a zwitterionic compound. The crystallization of amine clavulanate, for instance bis(2-(dimethylamino)ethyl)ether diclavulanate through the addition of (dimethylamino)ethyl)ether or N,N,N',N'-tetramethyl-1,2-diaminoethane diclavulanate or N,N,N',N'-tetramethyl-1,2-diaminoethane monoclavulanate through the addition of N,N,N',N'-tetramethyl-1,2-diaminoethane as described in EP-647229B can advantageously take place by just adding clavulanic acid

and amine, preferably both in an organic solvent, simultaneously to a crystallization vessel. Suitable organic solvents for the clavulanic acid solution are ethyl acetate, methyl acetate, propyl acetate, n-butyl acetate, methyl ethyl ketone, methyl isobutyl ketone and mixtures thereof. The amine is advantageously mixed with alcohols, nitriles, ketones, esters and mixture thereof. The present invention also covers the conversion of amine clavulanate prepared in this way into potassium clavulanate.

The invention will now be described with reference to the following examples, which are not to be constructed as being limiting the invention, but are provided purely for illustrative purposes.

Example 1

Preparation of crystalline 7ß-amino-3'-desacetoxycephalosporanic acid from an enzymatic hydrolysis of 7ß-phenylacetamido-3'-desacetoxyceph-3-em-4-carboxylic acid.

Enzymatic conversion:

7ß-Phenylacetamido-3'-desacetoxycephalosporanic acid (80 g, 0.24 mole) and sodium metabisulfite (1 g, 0.005 moles) were suspended in water (0.62 l) in a three-necked round bottom flask equipped with a stirrer, a pH-electrode and a dropping funnel filled with ammonium hydroxide (25% in water, w/w).

With stirring, the temperature of the suspension was raised to 30°C. In 15 minutes, the pH was adjusted to 8.4 by the addition of ammonium hydroxide as a result of which the suspension dissolved into a clear solution. Immobilized Alcaligenes faecalis penicillin-G acylase, as described in International patent application WO 9704086 (30 g, weighed after filtering and washing the beads with water) was added, the total volume was adjusted to 1.0 litre, and the mixture was stirred at 30°C for 4 hours at a stirring speed of approximately 50 rpm. During this process the pH was maintained at 8.4

by gradually adding ammonium hydroxide from the dropping funnel. The immobilized enzyme was removed by filtration and the beads were washed with water (0.1 l). The filtrate and washings were combined and further used in the next step.

Extraction

A two litre three-necked round bottom flask equipped with a stirrer, a pH-electrode and a dropping funnel filled with hydrochloric acid (36% in water, w/w) was charged with isobutanol (0.25 l) and hydrochloric acid (0.065 l). At 30°C, the 7-ADCA and phenylacetic acid containing solution obtained after the enzymatic conversion was added in 15 minutes under stirring. During this process the pH of the mixture was maintained at 0.5 by gradually adding hydrochloric acid from the dropping funnel. The mixture was transferred to a separating funnel and the aqueous phase was isolated and extracted with isobutanol (0.25 l). Both isobutanol phases were combined and extracted with water (0.1 l). Both aqueous phases were combined.

A second two litre three-necked round bottom flask equipped with a stirrer, a pH-electrode and a dropping funnel filled with ammonium hydroxide (25% in water, w/w) was charged with water (0.065 l). At 30°C, the combined 7-ADCA containing aqueous phases were added in 15 minutes under stirring. During this process the pH of the mixture was maintained at 7.8 by gradually adding ammonium hydroxide from the dropping funnel. The mixture was transferred to a separating funnel, the aqueous phase was isolated to be used in the next step, and the isobutanol phase was discarded.

Crystallization

A two litre three-necked round bottom flask equipped with a stirrer, a pH-electrode and a dropping funnel filled with aqueous sulphuric acid (6N) was charged with water (0.065 l). At 30°C, the 7-ADCA containing aqueous phase obtained after extraction was added in 30 minutes under stirring. During this process the pH of the mixture was maintained at 5.1 by gradually adding sulphuric acid from the dropping funnel. When addition was completed, the pH of the suspension was lowered to 3.6 by the addition of

sulphuric acid and the temperature was lowered to 2°C. Stirring was continued for 30 minutes.

Isolation

The 7-ADCA crystals obtained above were isolated by filtration using a glass sintered funnel and washed with water (0.25 l). The white 7-ADCA crystals were dried at 50°C until a constant weight of 45 g (purity 99%, 0.21 moles, yield 87.5%) was reached.

Example 2

Preparation of crystalline ampicillin trihydrate from an aqueous solution containing ampicillin hydrochloride by simultaneous addition of base etc.

A crystallization vessel containing cold water (0.3 l) and equipped with a stirrer, a pH-electrode and a dropping funnel filled with ammonium hydroxide (25% in water, w/w), was charged with an aqueous solution containing 15% (w/w) ampicillin hydrochloride (0.15 l). A few crystals of ampicillin trihydrate were added and after stirring for 5 minutes, an aqueous solution containing 15% (w/w) ampicillin hydrochloride (2.85 l) was added in 45 minutes under stirring and the pH of the reaction mixture was maintained at 5.5 by gradually adding ammonium hydroxide from the dropping funnel. When the addition was completed, the mixture was stirred for 5 minutes. The pH of the suspension was lowered to 4.9 by the addition of hydrochloric acid (2M). After lowering the temperature to 0°C, stirring was continued for 2 hours. The crystals were collected by filtration, washed with acetone and dried to give ampicillin trihydrate in a yield of 92%.

The concordance value of crystalline ampicillin trihydrate was less than 1 mol %.

Comparison with the preparation of crystalline ampicillin trihydrate by adding a base to a solution of ampicillin hydrochloride.

Ammonium hydroxide (25% in water, w/w) was added gradually to an aqueous solution containing 15% (w/w) ampicillin hydrochloride (0.15 l) under

stirring till the pH was raised from 1.5 to 5.1. At pH = 2.5, some crystalline ampicillin trihydrate were added as seed. The crystalline slurry was stored overnight at 0°C and, then, the crystals were collected by filtration, washed with acetone and dried to give ampicillin trihydrate.

The concordance value of the crystalline ampicillin trihydrate is 4-8 mol % after repetition of a number of experiments.

Example 3

Crystallisation of bis(2-(dimethylamino)ethyl)ether clavulanate from a clavulanic acid solution by simultaneous addition of clavulanic acid and bis(2-(dimethylamino)ethyl)ether

Ethanol (50 ml) was placed into a one litre three-necked round bottom flask fitted with a thermometer, two dropping funnels and a stirrer. The temperature was brought to 10°C and under stirring an impure solution of clavulanic acid (400 ml; 32.9 g clavulanic acid/litre) in ethyl acetate and a solution of bis(2-(dimethylamino)ethyl)ether (13.5 g) in ethanol (230 ml) were added simultaneously during 15-20 minutes at 10-15°C. After the addition the mixture was stirred for one hour at 5°C. The crystals were filtered, washed twice with ethyl acetate 40 ml) and dried under vacuum at room temperature. Bis(2-(dimethylamino)ethyl)ether diclavulanate (15.97 g; purity = 95%) in a yield of 80% was obtained.

Example 4

Crystallisation of bis(2-(dimethylamino)ethyl)ether clavulanate from a clavulanic acid solution by simultaneous addition of clavulanic acid and bis(2-(dimethylamino)ethyl)ether

The following experiment was carried out under nitrogen atmosphere. A volume of 250 ml of dry ethyl acetate was added to an empty vessel. Then, in approximately 5 minutes under vigorous stirring simultaneously 2 vol-% of

1000 ml of a solution of clavulanic acid in ethyl acetate, with a concentration of ca 40 g/l clavulanic acid, and 2 vol-% of a solution of 22.9 grams of amine in 250 ml ethyl acetate are added. The temperature during addition was 37°C. After crystallisation the remaining 98 vol-% of both clavulanic acid solution and amine solution were added in ratio in approximately 5 minutes. In the meantime, cooling was started to reach 18°C at the time the addition of the solutions was finished. Cooling was proceeded until 0 - 5°C and the crystal slurry was stirred at this temperature for one hour. The crystals were separated by filtration and washed twice with 100 ml ethyl acetate. The crystals were dried under vacuum atmosphere at room temperature to yield 64.3 g of bis(2-dimethylamino)ethyl) ether diclavulanate.The purity of the crystals was 62.7% based on clavulanic acid and the yield was 99.5%.

CLAIMS

1. A process to prepare a crystalline ß-lactam compound which comprises simultaneous addition of a solution of said ß-lactam compound and a corresponding titrant to a crystallization vessel to form a crystallization mixture and isolation of the crystalline ß-lactam compound.

2. A process according to claim 1 wherein a small amount of solvent or crystallization mixture is present in the crystallization vessel before the addition of the solution of the ß-lactam compound and the titrant.

3. A process according to any one of the claims 1-2 wherein the crystallization vessel is provided with seeding crystals.

4. A process according to any one of the claims 1-3 wherein the temperature of the crystallization vessel is maintained between 0°C and 50°C.

5. A process for the crystallization of a zwitterionic ß-lactam compound according to any one of the claims 1-4 wherein the pH-value is maintained between 2.5 and 7.5.

6. A process according to claim 5 wherein the pH-value is maintained between the isoelectric point of said ß-lactam compound and 7.5.

7. A process according to claims 1-6, which comprises the addition of an aqueous solution of the ß-lactam compound.

8. A process according to claims 1-7, which comprises the addition of a solution of a ß-lactam compound in a mixture of water and one or more organic solvents.

9. A process according to claims 1-8 wherein the titrant is an inorganic or organic acid or an inorganic or organic base.

10. A process according to claim 9 wherein the inorganic acid is selected from the group consisting of hydrochloric acid, sulphuric acid, nitric acid and phosphoric acid or the organic acid is formic acid or acetic acid.

11. A process according to claim 9 wherein an inorganic base is selected from the group consisting of sodium hydroxide, potassium hydroxide and ammonium hydroxide or the organic base is a monoamine or diamine.

12. A process according to claim 11, wherein the monoamine is selected from the group consisting of tertiary butylamine, tertiary octylamine, benzhydrylamine or the diamine is selected from the group consisting of N,N'-diisopropylethylenediamine, N,N,N',N'-tetramethyl-1,2-diaminoethane and bis(2-(dimethylamino)ethyl)ether.

13. A process according to claims 1-12 wherein the ß-lactam compound is chosen from the group consisting of amoxicillin, ampicillin, epicillin, cefaclor, cefadroxil, cefprozil, cefetamet, cefotaxim, cephalexin, cephaloglycin, cephradine, 6ß-aminopenicillanic acid (6-APA), 7ß-aminocephalosporanic acid (7-ACA), 7ß-amino-3-chloro-3-(desacetoxymethyl)cephalosporanic acid (7-ACCA), 7ß-amino-3'-desacetoxycephalosporanic acid (7-ADCA), 7ß-amino-3'-desacetylcephalosporanic acid (7-ADAC) and cephalosporin-C.

14. A process to prepare crystalline amine clavulanate according to anyone of the claims 1-3 which comprises simultaneous addition of a solution of clavulanic acid and an amine in an organic solvent and isolation of the crystalline amine clavulanate.

15. A process according to claim 14, wherein the solution of clavulanic acid is in ethyl acetate and the amine is bis(2-(dimethylamino)ethyl)ether in ethanol solution.

16. A process for the preparation of an alkali metal salt of clavulanic acid, which comprises the conversion of the amine clavulanate, prepared according to claim 14 or 15, to potassium clavulanate.

17. A process according to claim 16, which comprises the conversion of the amine clavulanate into potassium clavulanate by addition of potassium 2-ethylhexanoate.

18. Crystalline ß-lactam zwitterionic compound with an impurity level of the acidic addition salt of the corresponding ß-lactam compound of lower than 1% by weight.

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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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